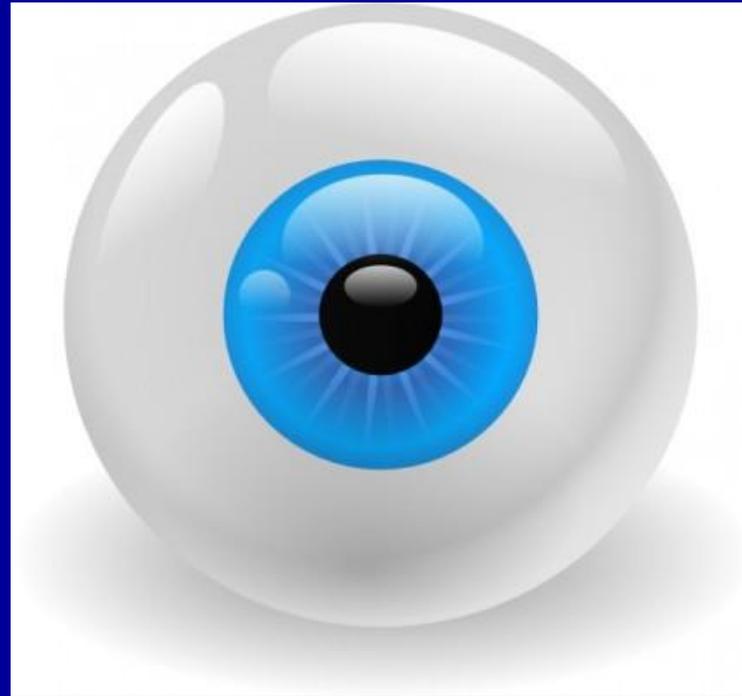


Challenges in Ophthalmology



Jay M. Stewart MD
Associate Professor

Ricardo Lamy MD, PhD
Assistant Professor

Department of Ophthalmology
University of California, San Francisco

UCSF

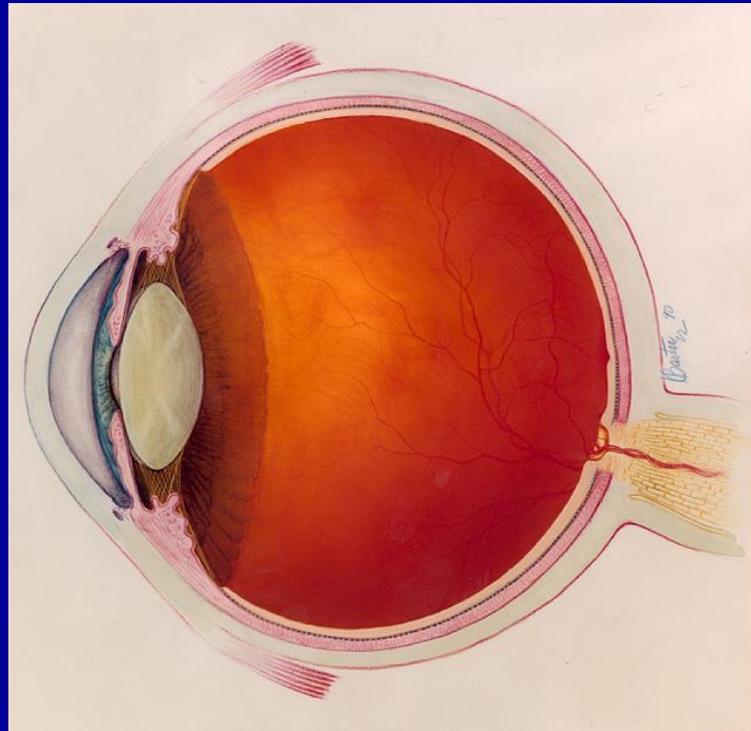


Outline

- Introduction to Eye Anatomy
- Selected Challenges in Ophthalmology
- Questions / Brainstorming

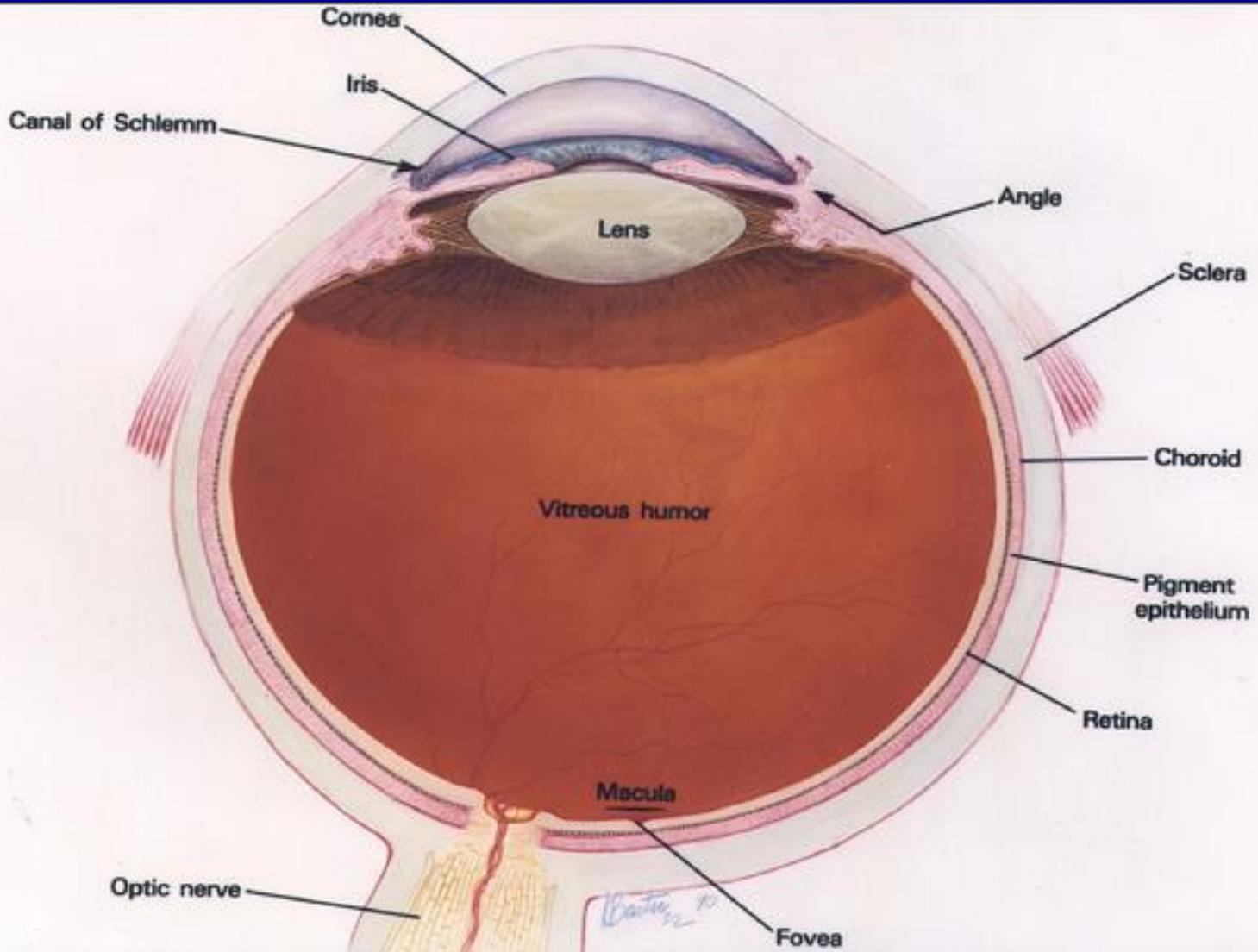
General Anatomy

- The eye has three distinct layers or “tunics”:
 - outer “fibrous” tunic (cornea and sclera)
 - middle “vascular” tunic (iris, ciliary body, and choroid)
 - inner “nervous” tunic (retina)



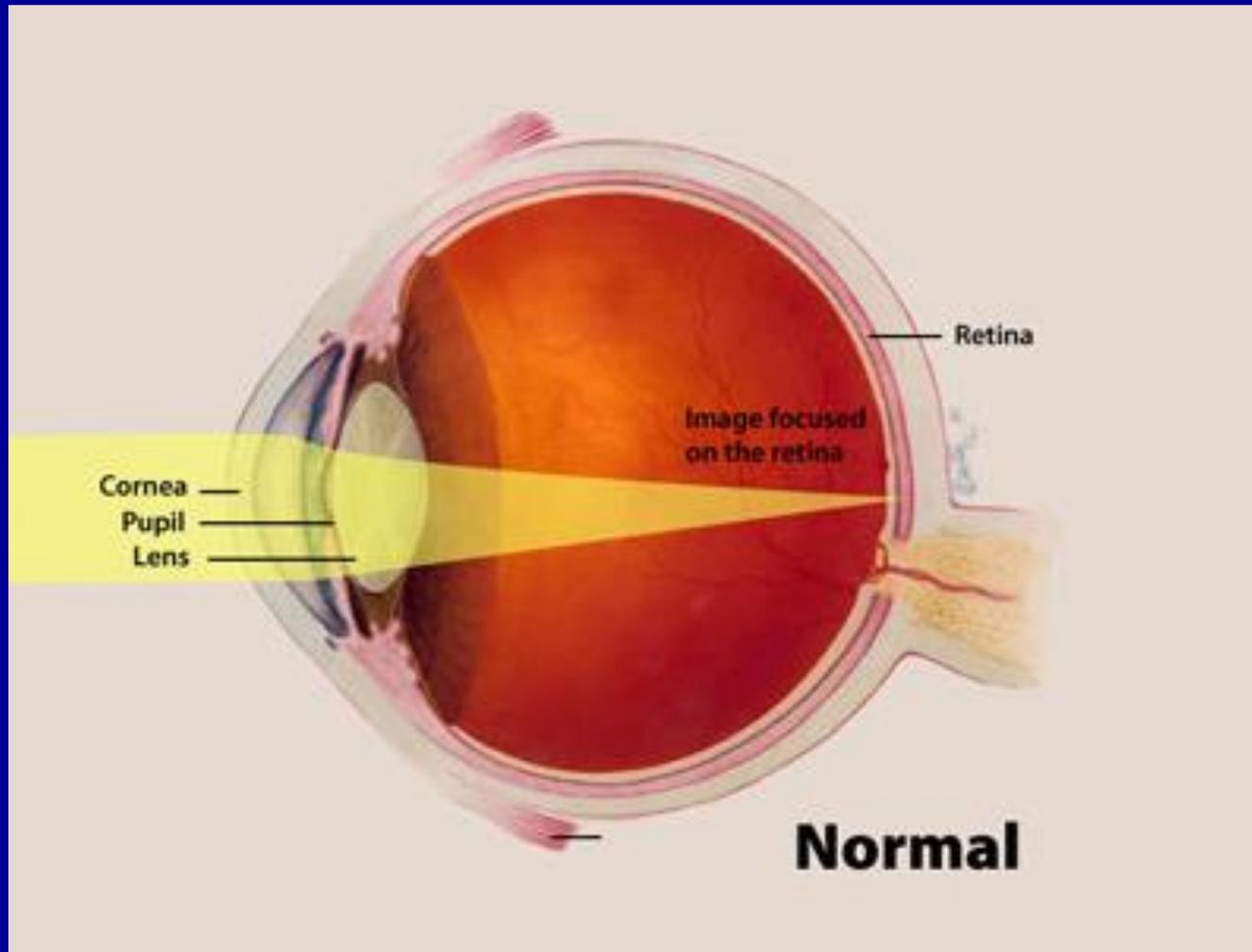
Source: NEI - NIH

General Anatomy



Source: NEI - NIH

Light Pathway

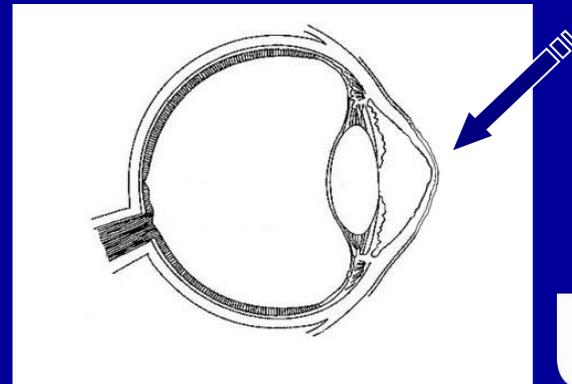
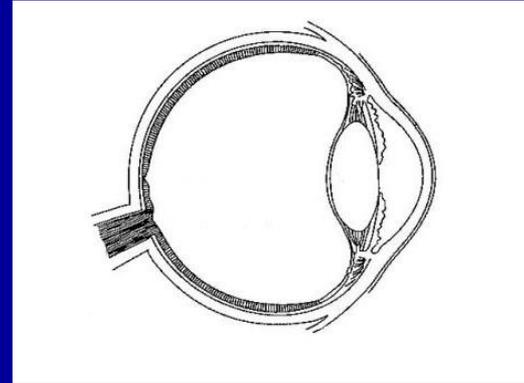


Source: NEI - NIH

Challenge #1

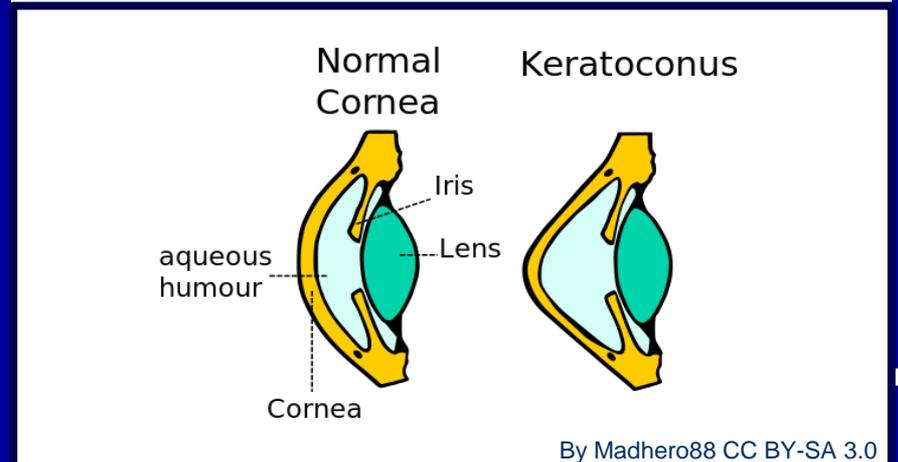
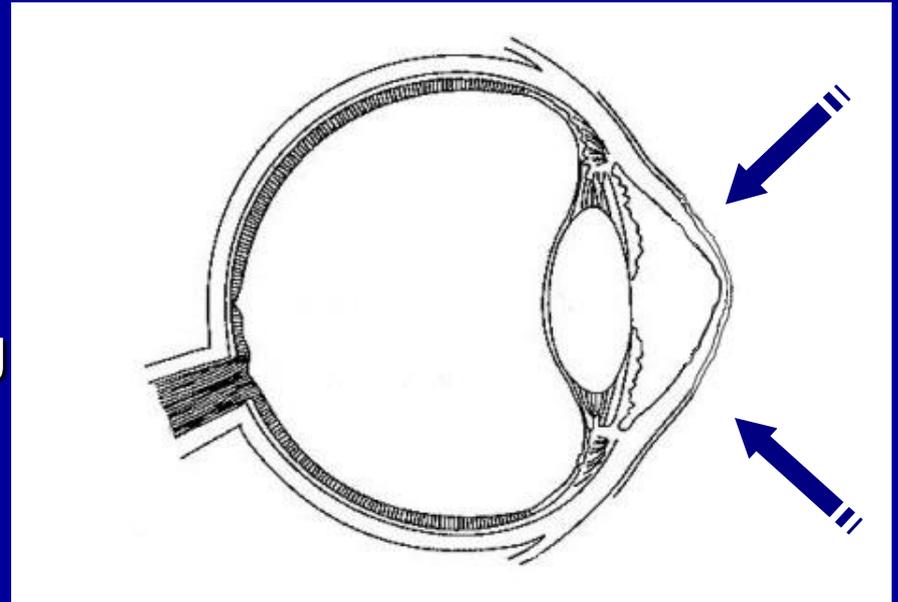
Corneal Ectasias

- Ectasia (distension or expansion of a hollow organ)
 - Keratoconus Disease
 - Post LASIK Ectasia



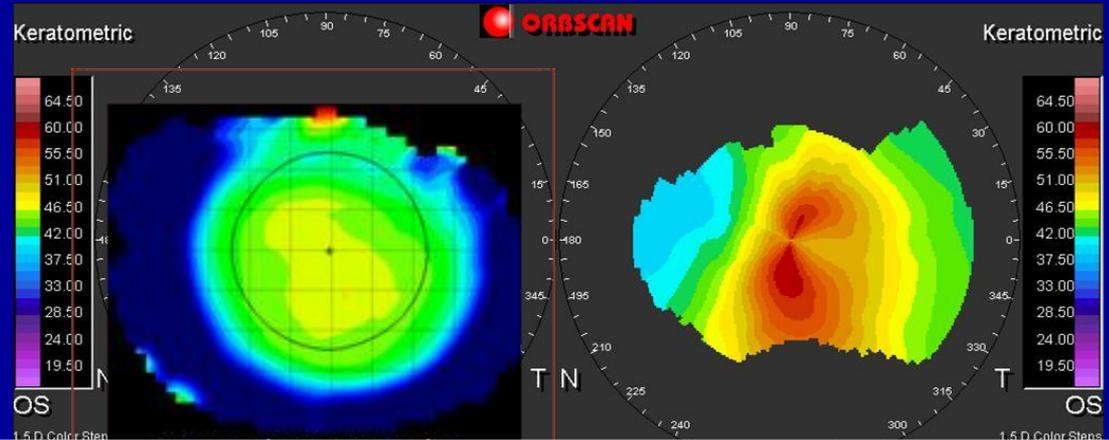
Keratoconus

- Corneal disease
- Unknown etiology
- Corneal protrusion and thinning
- Bilateral
- Asymmetric
- If left untreated, up to 20% of patients will require a corneal transplant



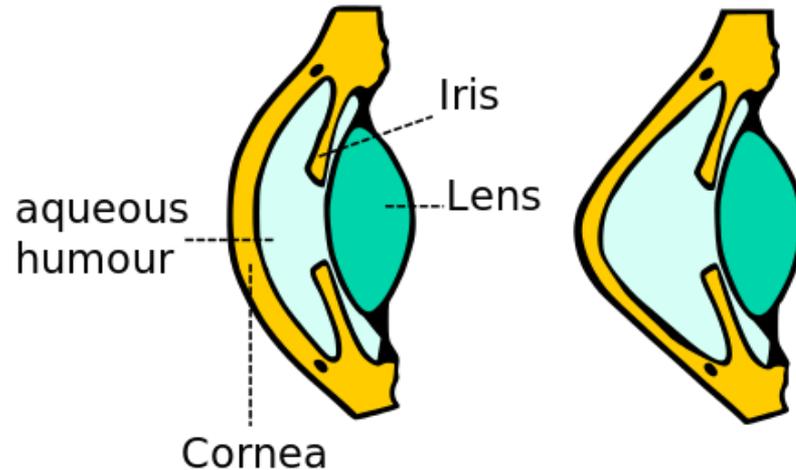
Diagnosis

- Topographical Maps
- Pachymetrical Maps (corneal thickness)



Normal Cornea

Keratoconus



Classical Treatments

- **Glasses**
- **Contact lens**
- **Corneal rings**
- **Keratoplasty (Corneal transplant)**

Keratoconus

**Genetic Predisposition
+
Environmental Stimuli**

Risk Factor

- Eye Rubbing

Protective Factors

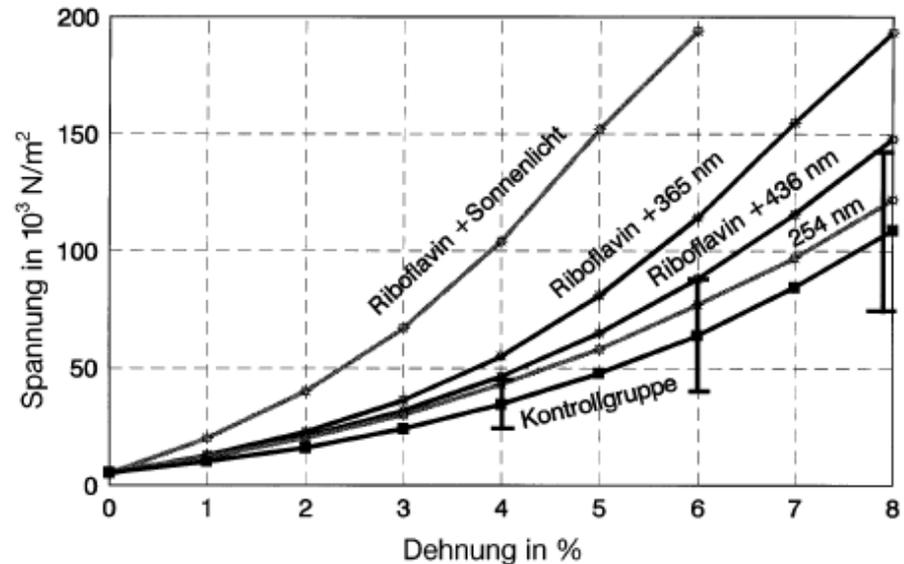
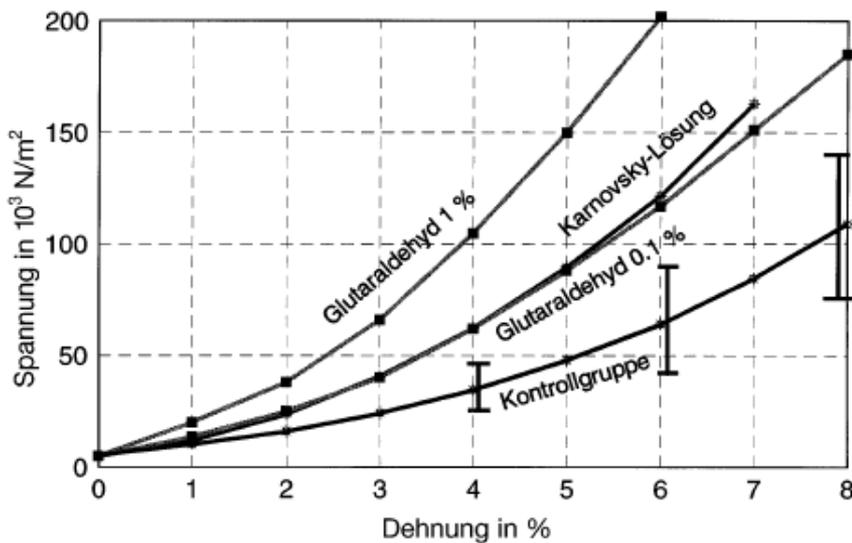
- Aging
- Smoking
- Diabetes

1970s

- Bailey AJ, *et al.* **Biological significance of the intermolecular crosslinks of collagen.** *Nature.* 1974; 251:105-9.
- Robert L, *et al.* **Biochemical study of the keratoconus.** *Arch Ophthalmol Rev Gen Ophthalmol.* 1970; 30(8):590-608.
- Cannon DJ, *et al.* **Collagen crosslinking in keratoconus.** *Invest Ophthalmol Vis Sci.* 1978;17(1):63-5.

1990s

- **Chemical:** Glutaraldehyde; Karnovsky Solution
- **Photochemical:** Riboflavin + Light

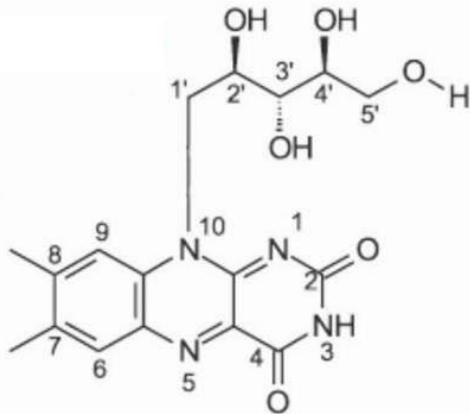


- Seiler T, Spoerl E, Huhle M, Kamouna A. Conservative therapy of keratoconus by enhancement of collagen cross-links. Invest Ophthalmol Vis Sci. 1996;37:S1017.
- Spörl E, Huhle M, Kasper M, Seiler T. Erhöhung der Festigkeit der Hornhaut durch Vernetzung. Ophthalmologe. 1997; 94:902-6.

Riboflavin (Vit. B2)

1879 – Lactochrome (Alexander Blyth)

1934 – Synthesized (Richard Kuhn)



Riboflavin

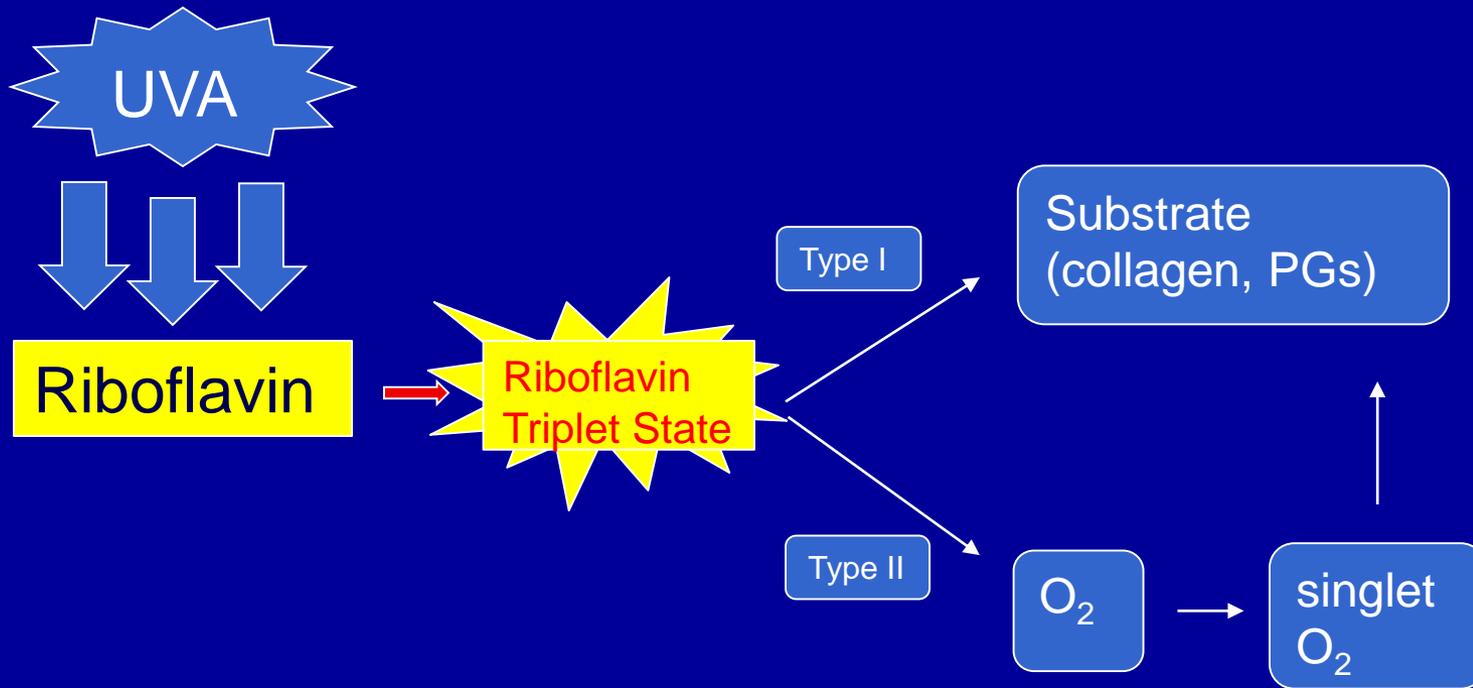
Formula: C₁₇H₂₀N₄O₆

IUPAC ID: 7,8-Dimethyl-10-[(2S,3S,4R)-2,3,4,5-tetrahydroxypentyl]benzo[g]pteridine-2,4-dione

Molar mass: 376.36 g/mol

Melting point: 536° F (280° C)

Photochemical Cross-linking



Generates cross-links not only between collagen molecules but also between proteoglycan core proteins

2003 - Germany

Riboflavin/Ultraviolet-A–induced Collagen Crosslinking for the Treatment of Keratoconus

GREGOR WOLLENSAK, MD, EBERHARD SPOERL, PhD, AND THEO SEILER, PhD, MD

2006 - Italy

J CATARACT REFRACT SURG - VOL 32, MAY 2006

Parasurgical therapy for keratoconus by riboflavin–ultraviolet type A rays induced cross-linking of corneal collagen

Preliminary refractive results in an Italian study

Aldo Caporossi, MD, Stefano Baiocchi, MD, Cosimo Mazzotta, MD, Claudio Traversi, MD, Tomaso Caporossi, MD

Corneal Collagen Crosslinking (CXL)

- Stops Progression in > 92% of patients
- Mild Improvement in Vision

2008 – Brazil & Australia

Reticulação do colágeno corneano com radiação ultravioleta e riboflavina para tratamento do ceratocone: resultados preliminares de um estudo brasileiro

Corneal collagen crosslinking with riboflavin and ultraviolet radiation for keratoconus treatment: preliminary results of a Brazilian study.

A Randomized Controlled Trial of Corneal Collagen Cross-linking in Progressive Keratoconus: Preliminary Results

Christine Wittig-Silva, MD; Mark Whiting, FRANZCO; Ecosse Lamoureux, PhD; Richard G. Lindsay, BScOptom; Laurie J. Sullivan, FRANZCO; Grant R. Snibson, FRANZCO

04/18/2016

FDA approves Corneal Crosslinking for treating progressive Keratoconus

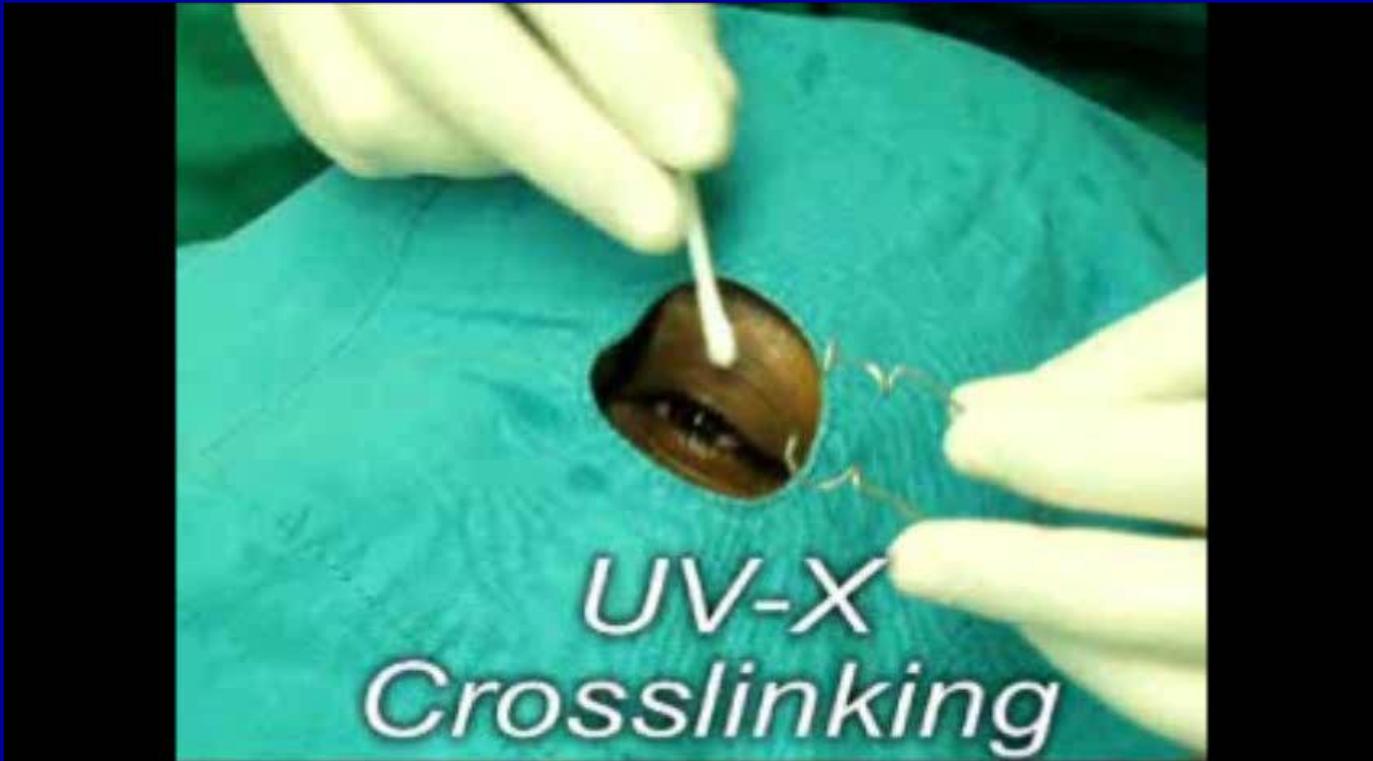


Corneal Collagen Crosslinking (CXL)



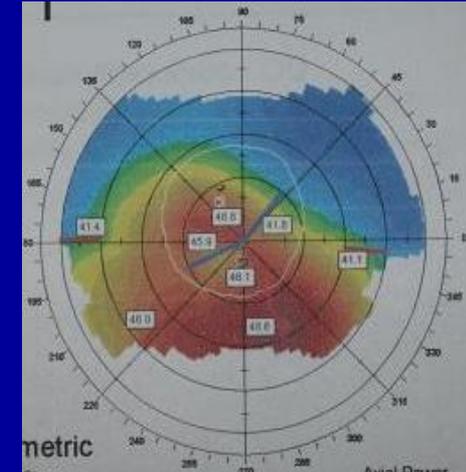
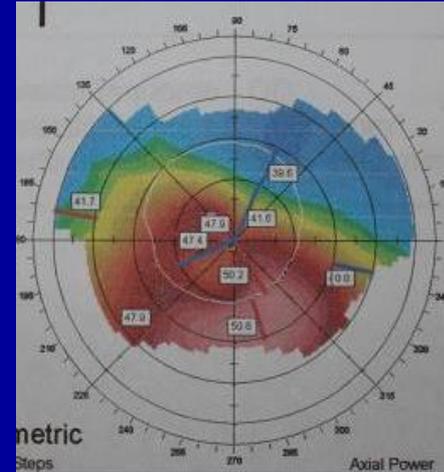
- Remove the corneal epithelium
- Apply riboflavin drops every 2 minutes for 30 min to saturate the cornea
- UVA 3 mW/cm² for 30 minutes

Video

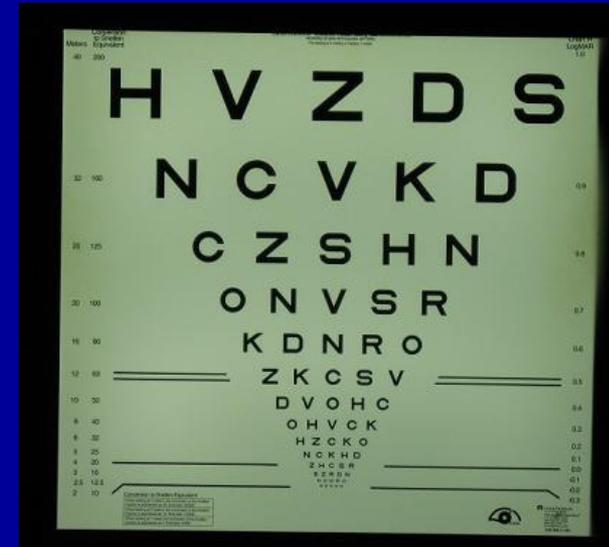


What to expect?

- Topography flattening
(Decreasing KMAX: 0.7 to 2.0 diopters)



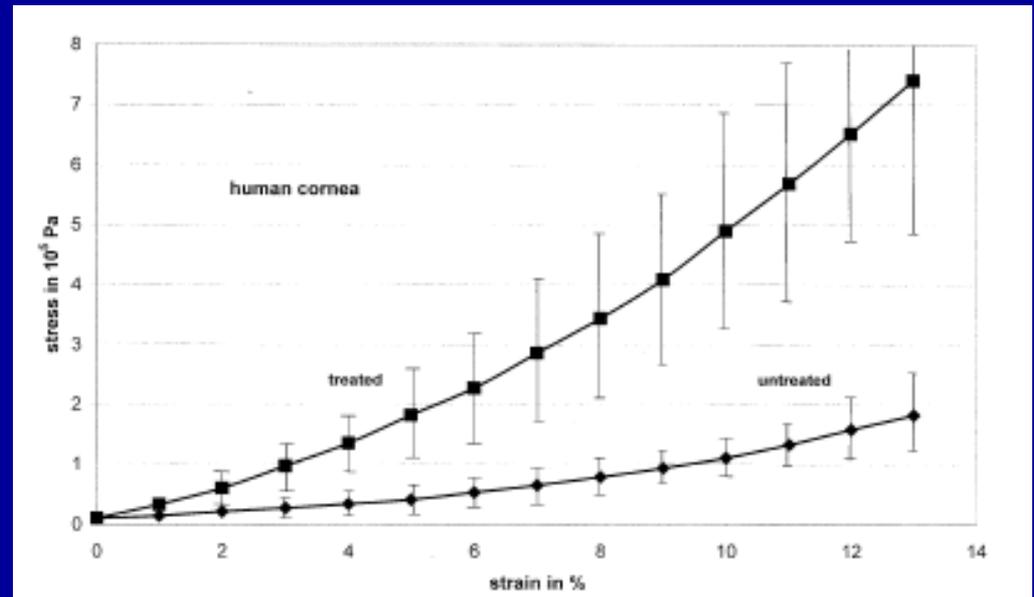
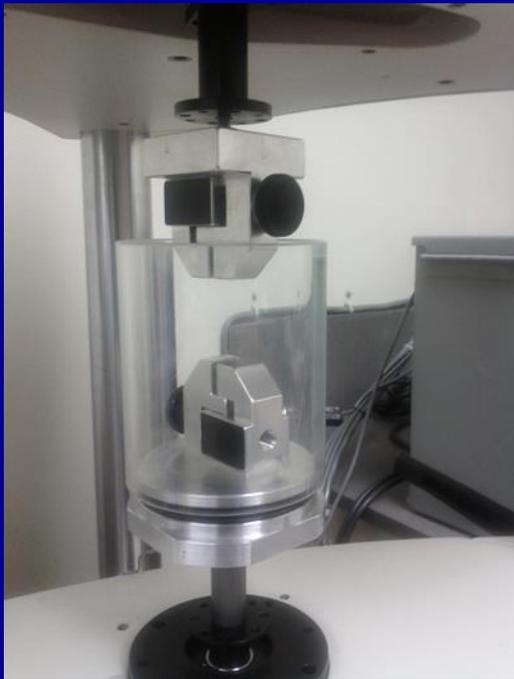
- Vision improvement
(BSCVA: 0.5 to 1.5 Snellen lines)



Biomechanical Effects

Ex Vivo

Uniaxial Test

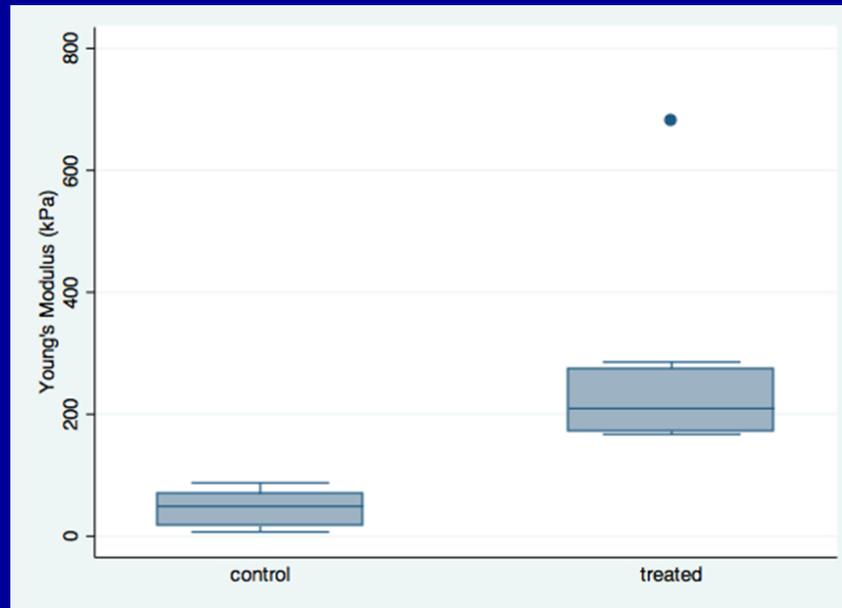


Wollensak G, Spoerl E, Seiler T.. *J Cataract Refract Surg* 2003; 29:1780–5

Biomechanical Effects

Ex Vivo

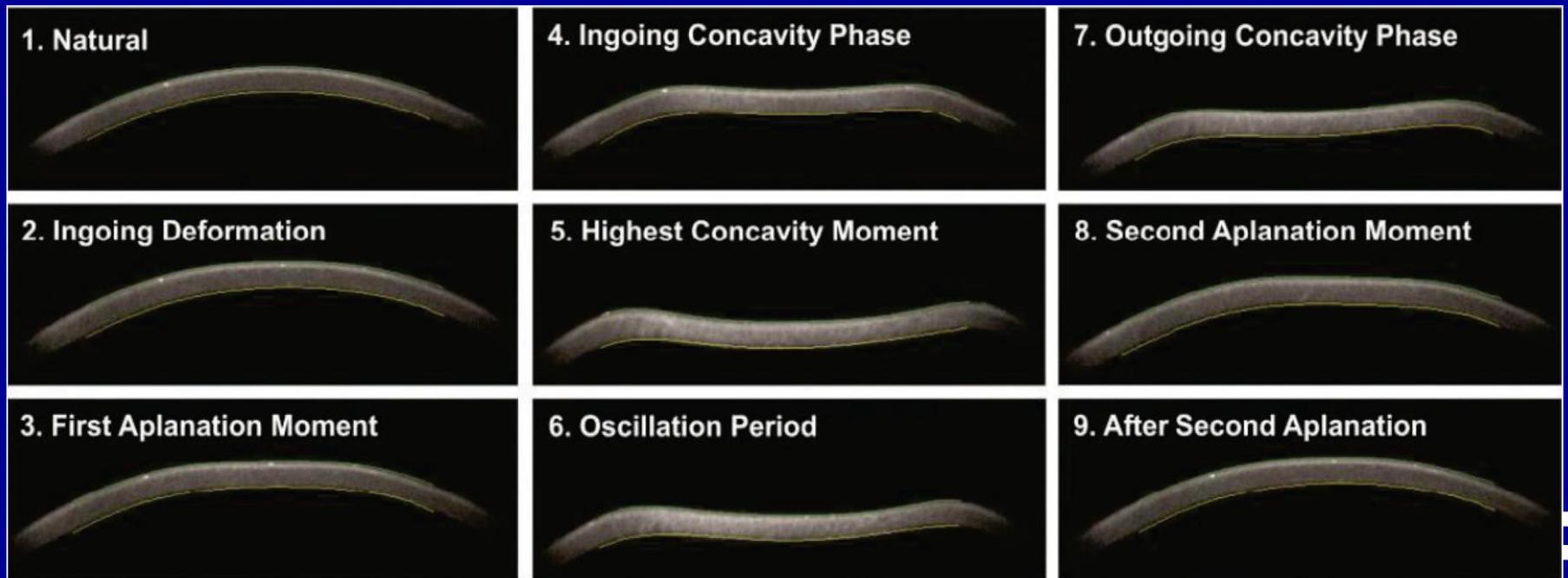
AFM Nanoindentation



Biomechanical Effects *In Vivo*

CORVIS ST[®]

- Air Jet
- High Speed Camera
- Analyze Corneal Deformation



Biomechanical Effects

In Vivo

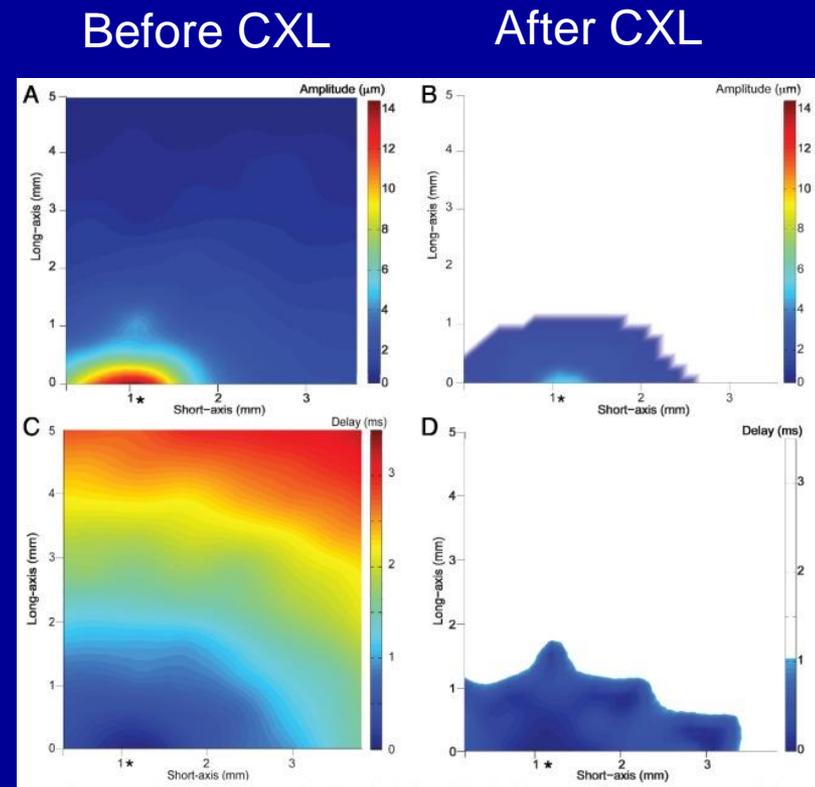
CORVIS ST[®]

- Confounded by biomechanical responses from surrounding tissues.
- Airjet displaces the aqueous fluid within the anterior chamber causing movement of the iris and lens, as well as the entire eye into the orbit.

Biomechanical Effects *In Vivo*

Optical Coherence Elastography

- Clinical devices are under development
- Micro Air-Pulse Stimulator (MAPS) to produce discrete tissue excitation that is synchronized with a high resolution phase-sensitive OCT imaging system

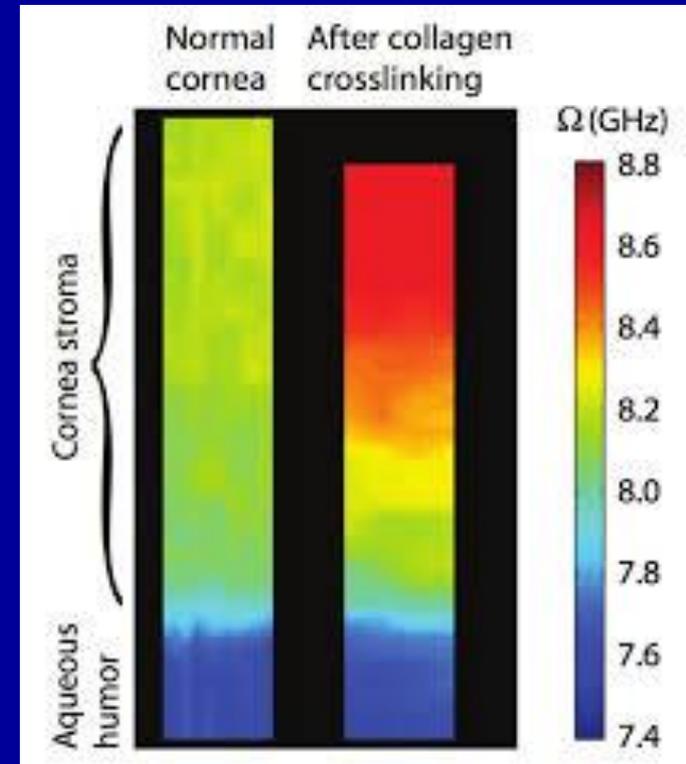


Twa et al. Biomed Opt Express. 2014 May 1; 5(5):
1419–1427

Biomechanical Effects *In Vivo*

Brillouin Microscopy

- Clinical devices are under development
- Continuous-wave laser light at 780 nm (0.7mW)
- Light Scattering



Scarcelli G, Yun SH.

http://crstodayeurope.com/pdfs/0315CRSTEuro_ES4_thompson.pdf

LASIK

Safety Guidelines

Corneal Thickness

- Pre-op $> 500 \mu\text{M}$
- Post-op $> 400 \mu\text{M}$ with a Residual Stromal Bed $> 250 \mu\text{M}$

Post-LASIK Ectasia incidence 0.05% to 0.25%

Form Fruste Keratoconus?

Forme Fruste Keratoconus (FFK)

- 10% of patients seeking LASIK are refused.
- 180,000 Keratoconus cases in America.
- 1 to 2% of the population may fit into the FFK or keratoconus suspect category. (3 to 6 Million patients in the USA are considered at risk if they were to seek LASIK consultation)

Challenge #2

Corneal Ulcers

- Microtrauma followed by infection = Infectious keratitis (corneal ulcers)
 - US: 75,000 per year
 - India: 840,000 per year
- Current Standard of Care
 - Topical antimicrobials
 - (up to 1 year may be required if *Acanthamoeba*)

What is the unmet clinical need?

- Blindness secondary to corneal ulcers
 - Resistant/aggressive infections
 - Patient compliance challenges
 - Lack of access to medications

1.5 - 2 million per year

Bulletin of the World Health Organization, 2001, 79: 214–221

Challenge #3

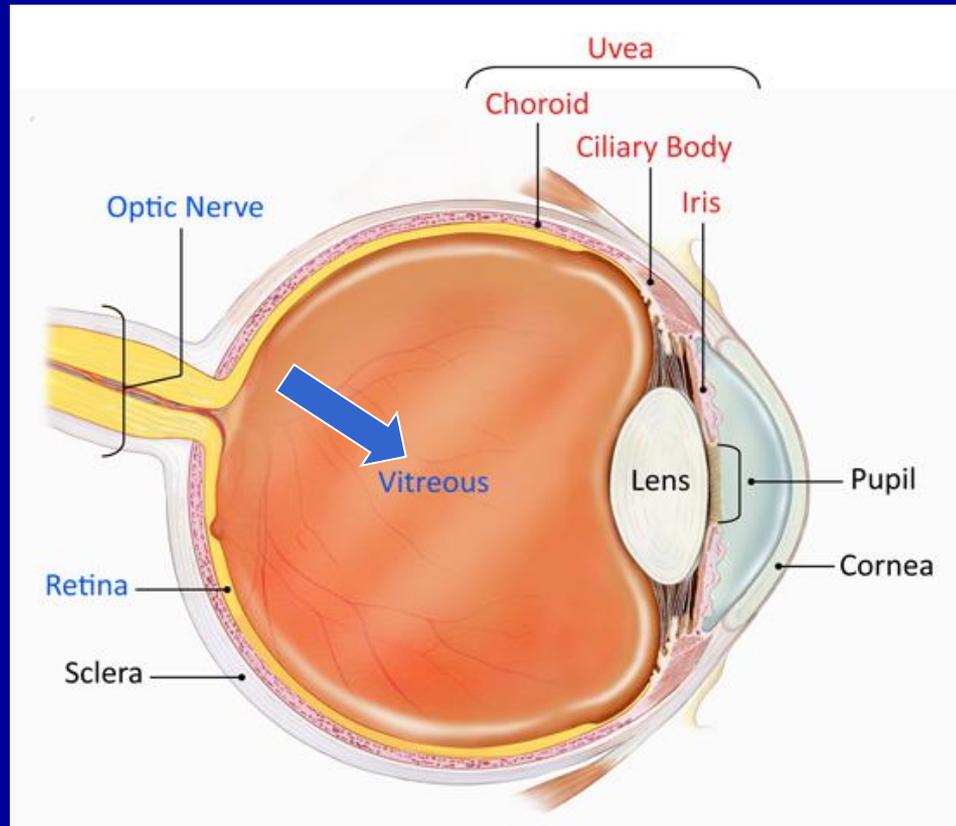
Floater



wikipedia.org/wiki/Floater

Vitreous Body

- 98% water
- 2% collagen and hyaluronan



Source: NEI - NIH

Floater

- **Primary**

- Light scattering in bundles of collagen fibers (crosslinking of collagen) and lacunae (liquid zones devoid of collagen fibrils)
- Crosslinking and vitreous liquefaction increases with age.

- **Secondary**

- Light scattering in proteins, amyloid or cells from vitreous hemorrhage, retinal tear, inflammatory conditions or intravitreal injections.

Prevalence of Symptoms

Prevalence of vitreous floaters in a
community sample of smartphone users.

Webb, Blake F., et al. *International journal of ophthalmology* 6.3 (2013): 402.

Up to 76% of smartphone users

Prevalence of Ultrasonic Findings

Table 1. Ultrasonic findings in the vitreous body at various ages

Age group	Patients	Eyes	Homogenous	Degeneration +	Degeneration + +
1-20	31	34	34	—	—
21-40	86	117	111/95 %	6/5 %	—
41-50	35	53	43/81 %	10/19 %	—
51-60	44	71	26/37 %	37/52 %	8/11 %
61-70	39	67	4/6 %	55/82 %	8/12 %
> 70	55	102	15/15 %	66/65 %	21/20 %
	290	444			

Oksala, Arvo. "Ultrasonic findings in the vitreous body at various ages." *Albrecht von Graefes Archiv für klinische und experimentelle Ophthalmologie* 207.4 (1978): 275-280.

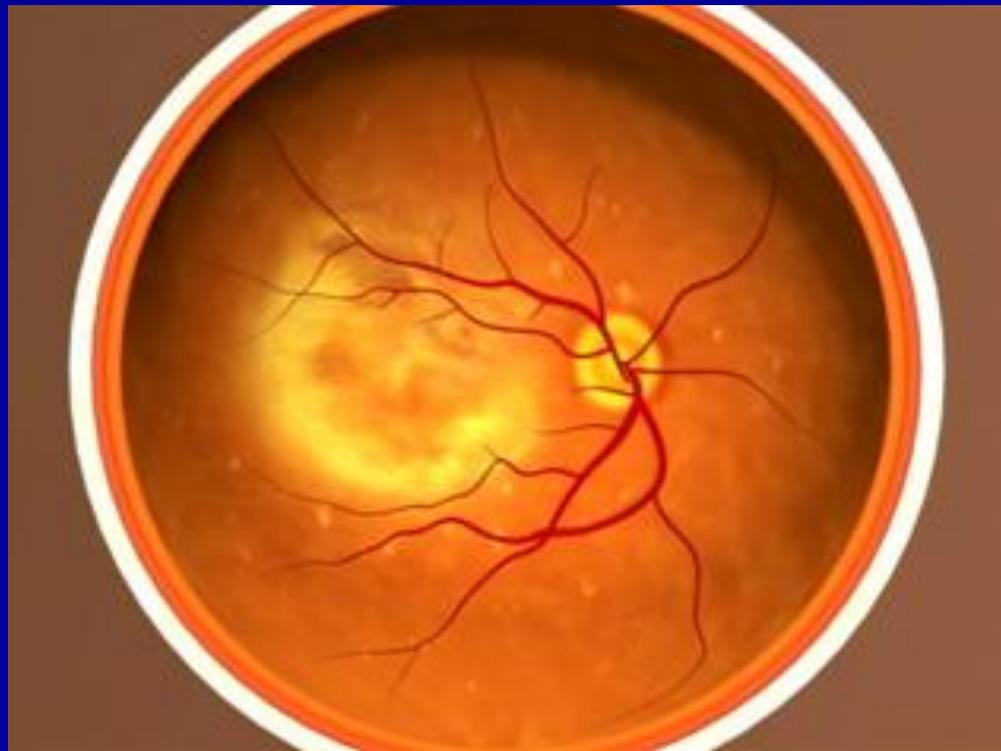
Treatment Options

- Vitrectomy – high success in removing the floaters, but increased risk of complications such as cataract, retinal tear, retinal hemorrhage.
- Yag Laser Vitreolysis – Can be used to treat opacities that are far from the retina. Lysis of fibers into smaller pieces or displacement from visual axis. Nothing is removed from the eye.
- Pharmacological Vitreolysis – 7 agents have failed. Ocriplasmin is the only one approved for vitreomacular adhesion

Challenge #4

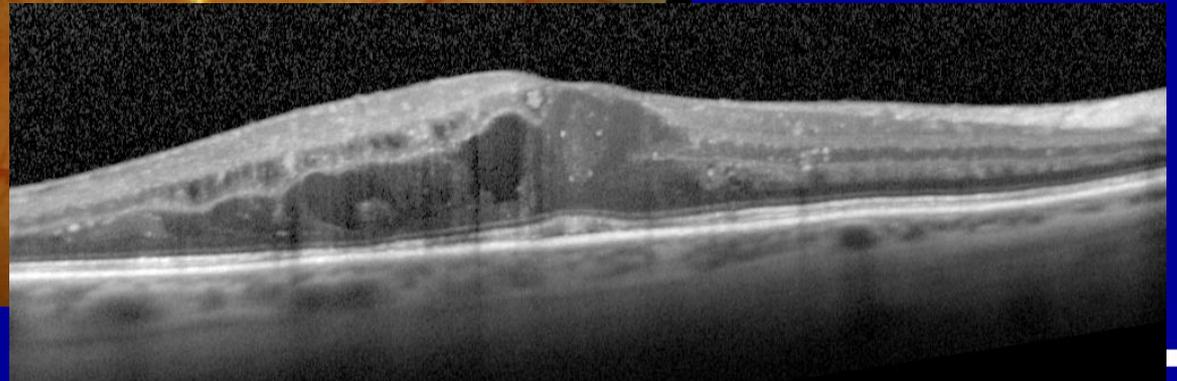
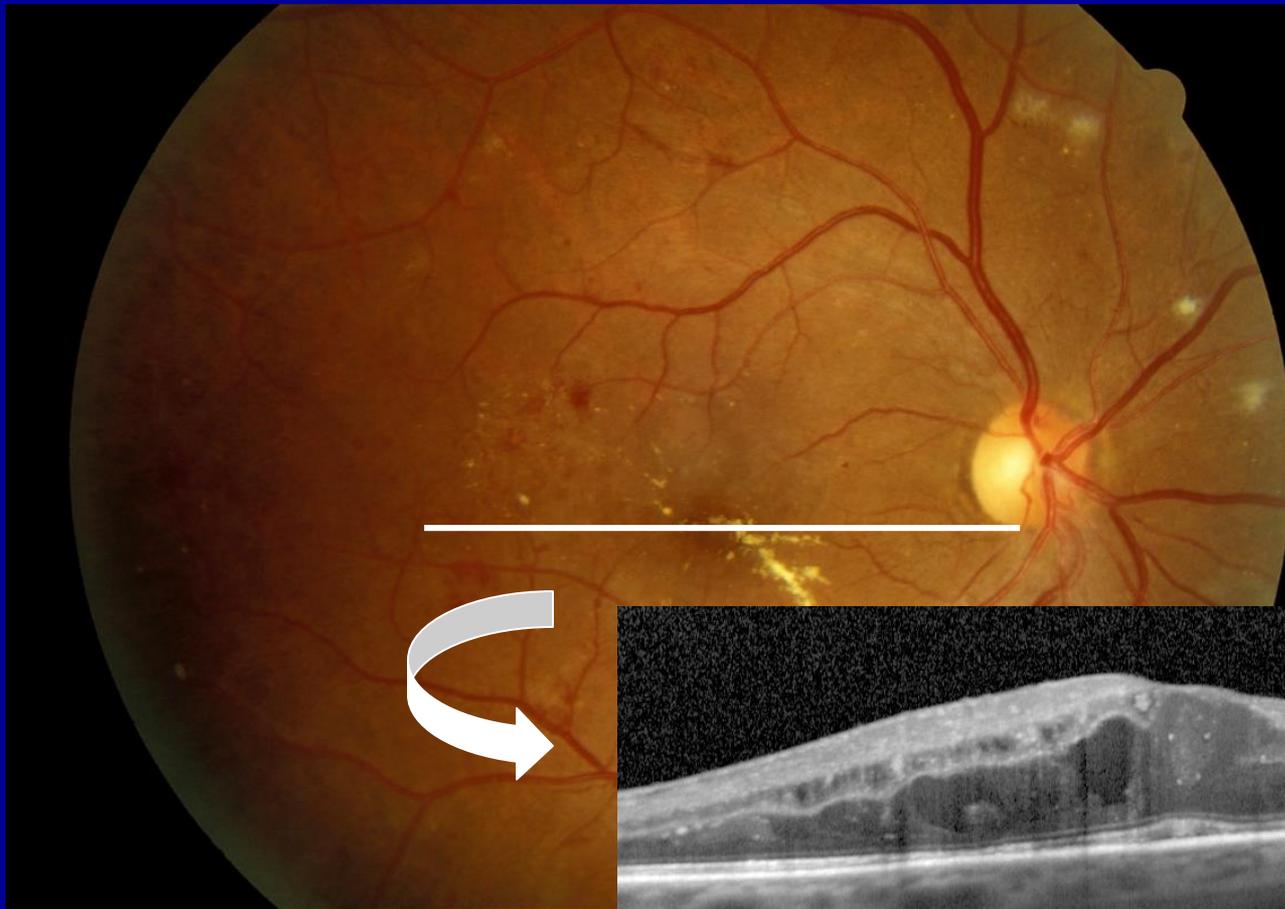
Intravitreal Medication Delivery

Age-related macular degeneration



Source: NEI - NIH

Diabetic macular edema

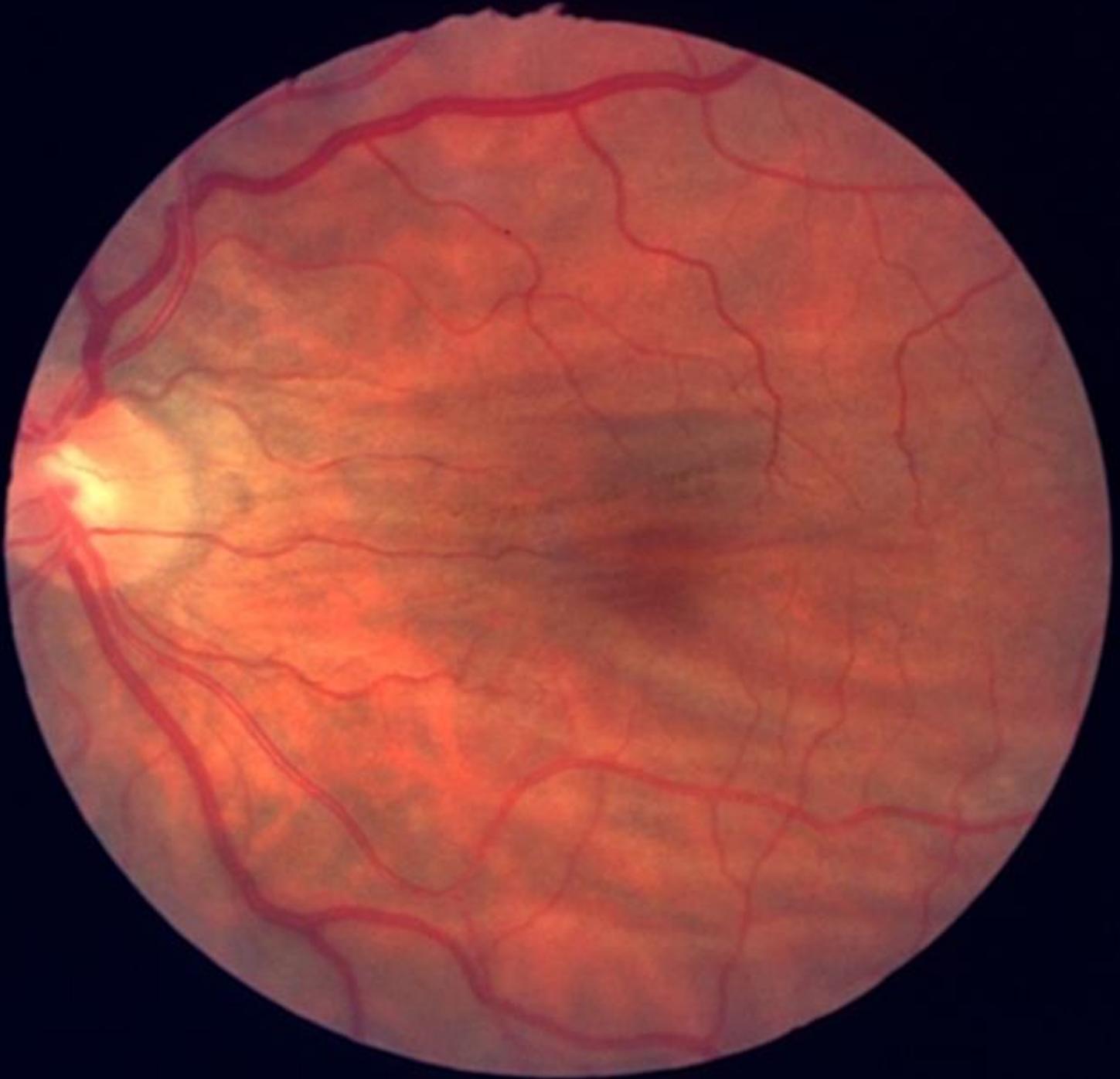


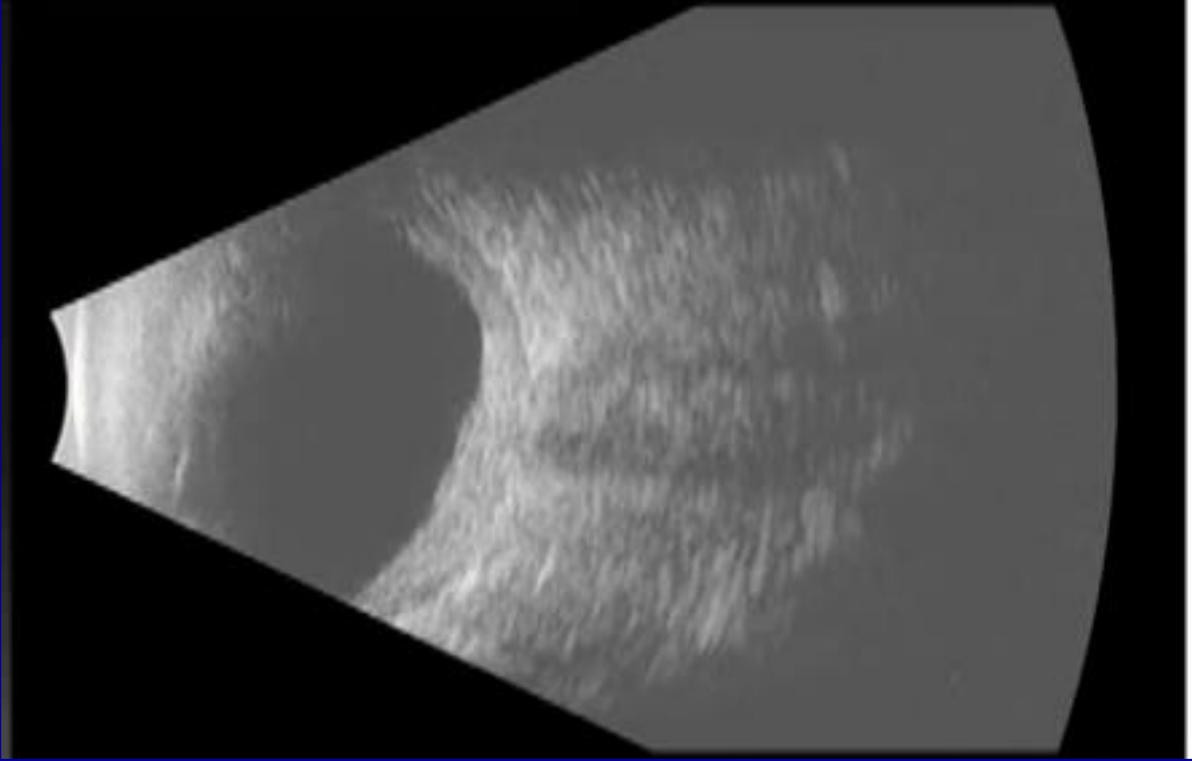


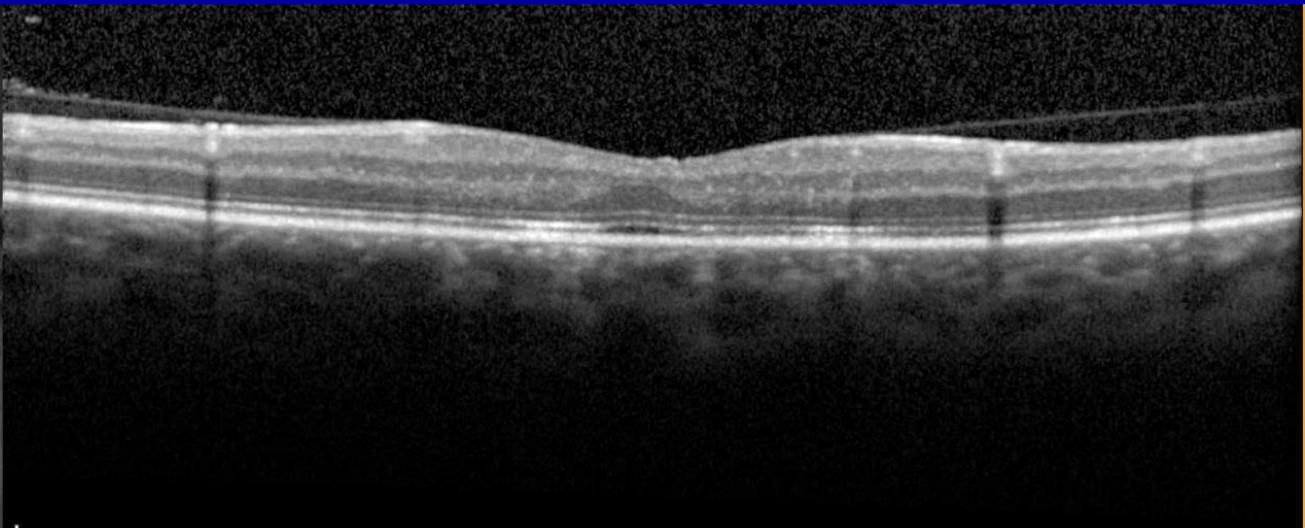
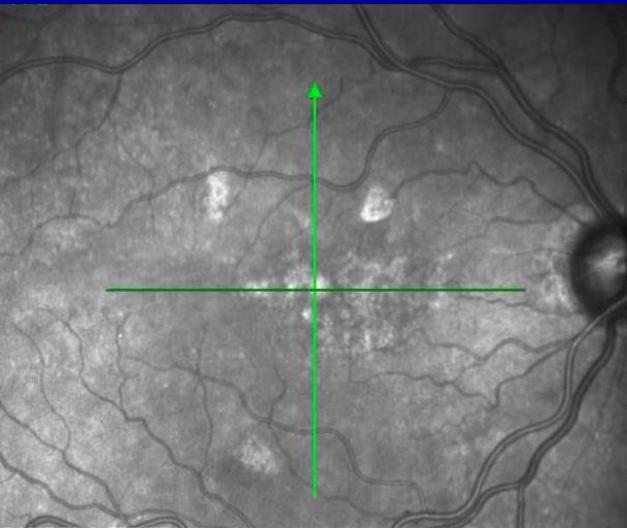
Challenge #5

Chronic Ocular Hypotony

- IOP < 5 mmHg
- Too little fluid production
or
- Too much fluid outflow







Challenge #6

Long-Duration Space Flights

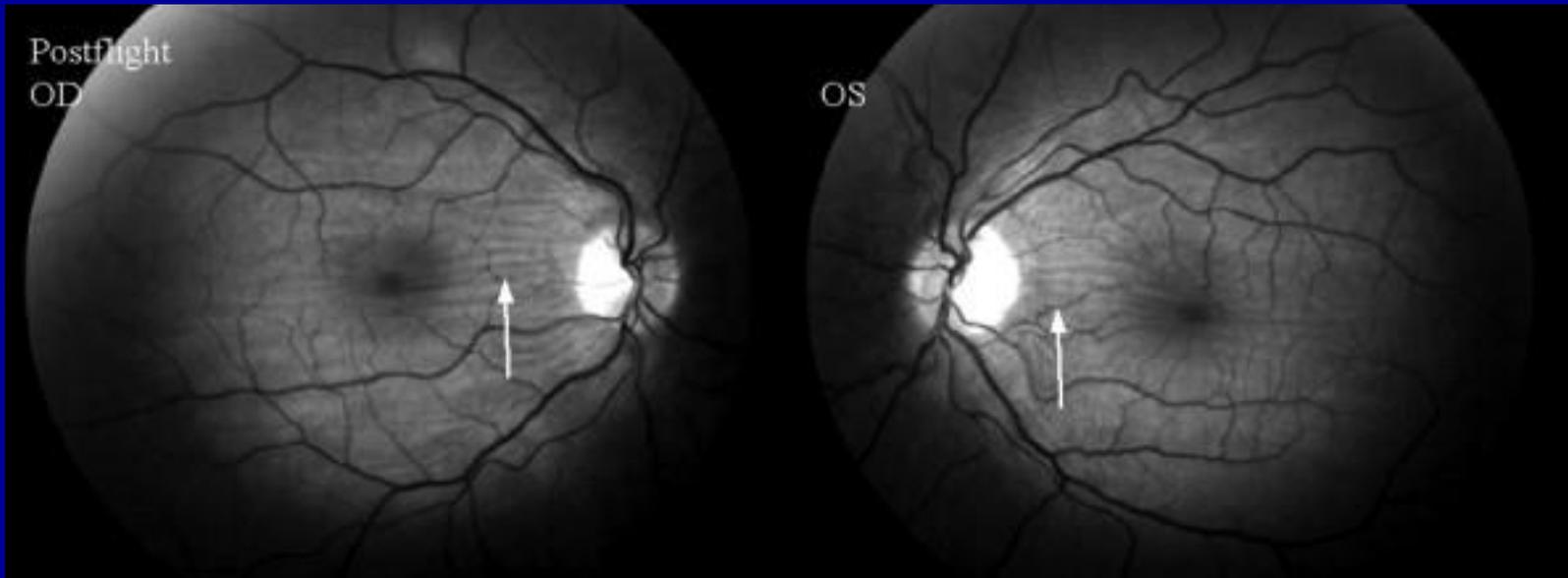
- Post-Flight CSF pressure is elevated in majority
- Loss of hydrostatic drainage
- Optic disc edema

Ophthalmic Changes

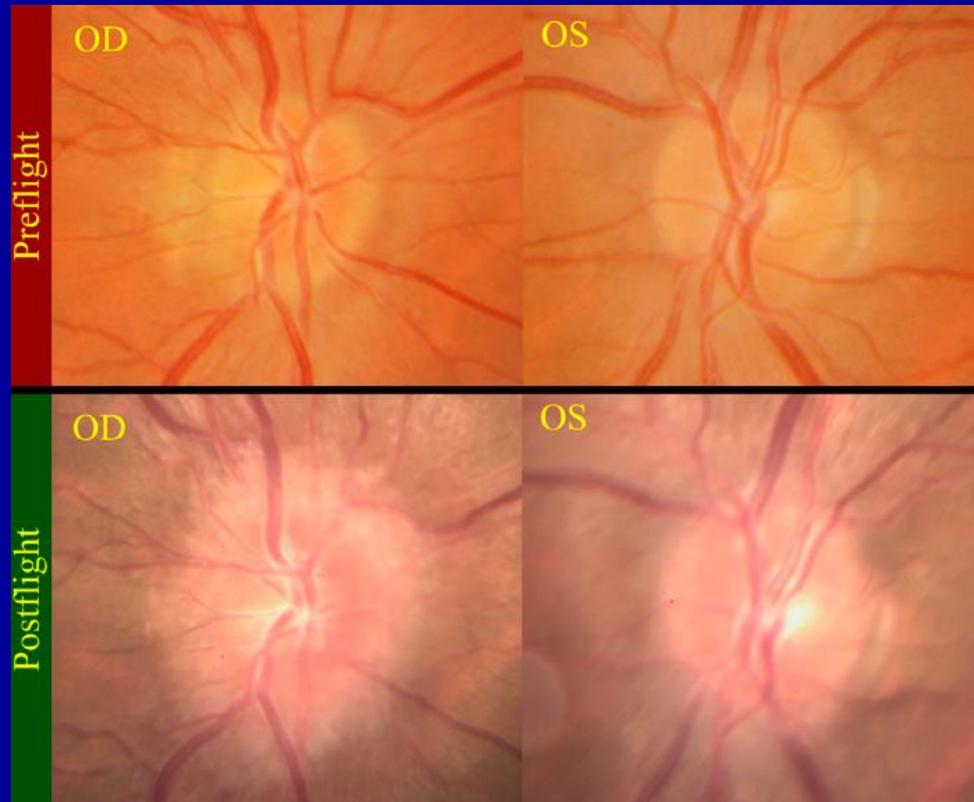
Table 2. Summary of ophthalmic changes from seven affected long-duration mission crewmembers. Data from [7,16].

Ophthalmic Condition	Total Affected
Optic nerve sheath distension	6/7 (86%)
Nerve fiber layer thickening	6/7 (86%)
Optic disc edema	5/7 (71%)
Posterior globe flattening	5/7 (71%)
Hyperopic shift in one or both eyes by $\geq +0.50$ diopters	5/7 (71%)
Choroidal folds	4/7 (57%)
Elevated postflight CSF pressure (indicative of increased <i>ICP</i>)	4/7 (57%)
Cotton wool spots	3/7 (43%)
Decreased intraocular pressure (<i>IOP</i>) postflight	3/7 (43%)
Tortuous optic nerve	2/7 (29%)

Nelson et al. *Life* 2014, 4(4), 621-665;



Mader et al. Ophthalmology 2011;118:2058-69

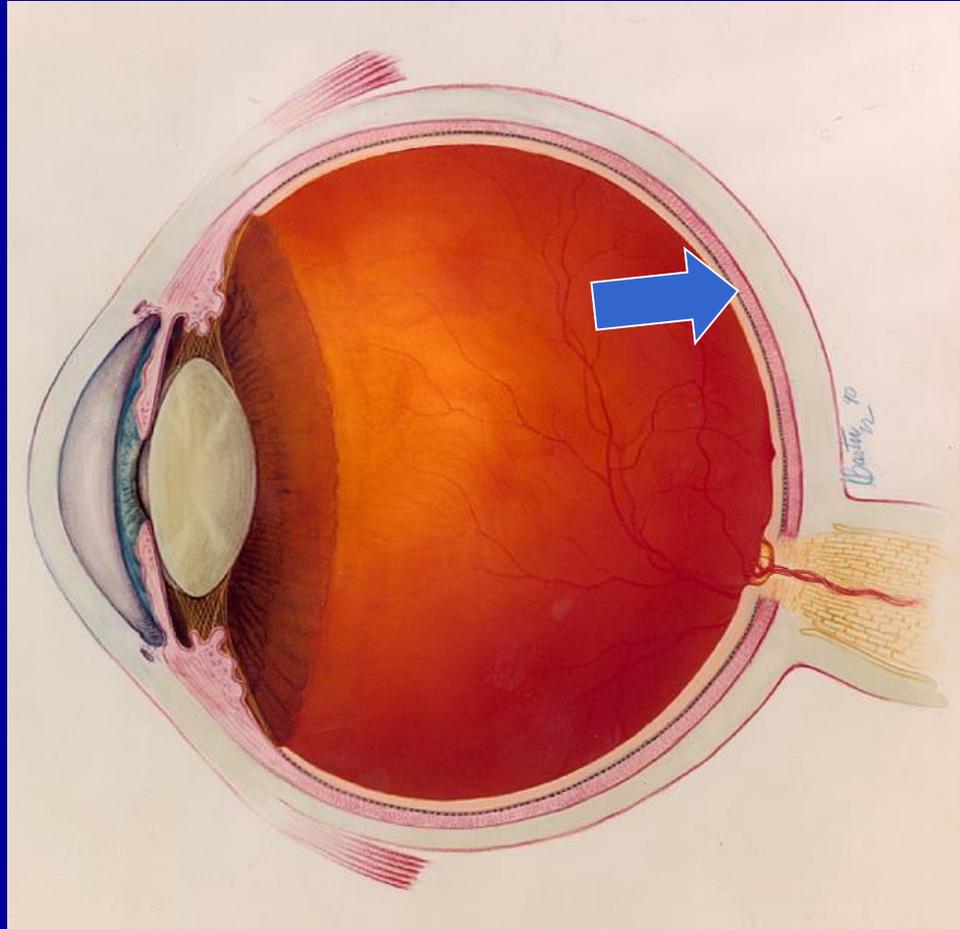


Nelson et al. Life **2014**, 4(4), 621-665;

Translaminar Pressure Gradient

- Normally: IOP ~5 mmHg more than ICP
 - IOP 15 mmHg vs ICP 10 mmHg
- Space Flights (reversed)
 - IOP 15 mmHg vs ICP 20 mmHg
- IOP: intraocular pressure
- ICP: intracranial pressure

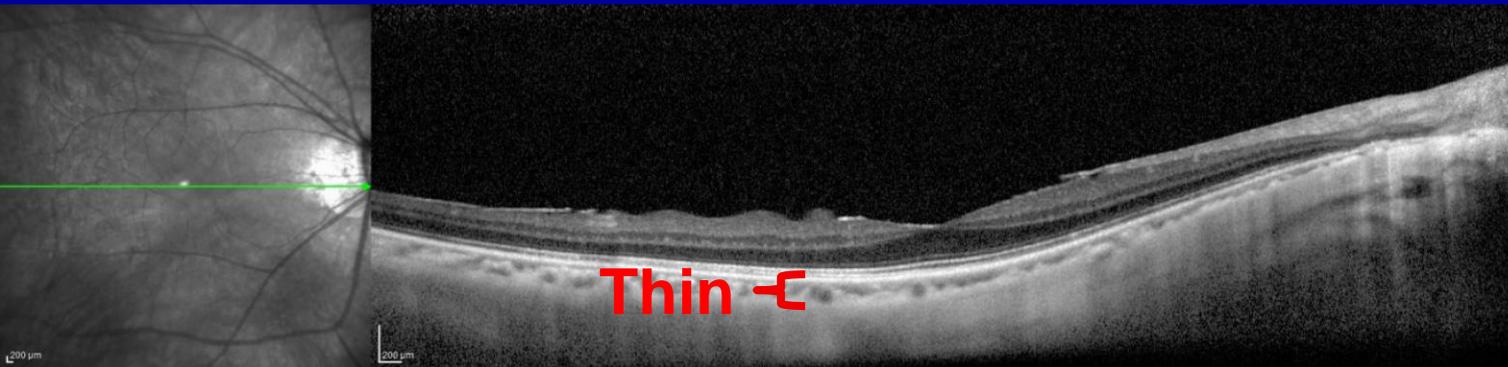
Choroidal thickening



Source: NEI - NIH

Choroidal thickening

- All have Choroidal Thickening in Flight



Choroidal thickening

- Post flight, some cases return and even get thinner choroidal measurements; other cases never return to baseline

Challenges

- Corneal ectasias
- Corneal ulcers
- Floaters
- Intravitreal drug delivery
- Ocular hypotony
- Long-duration space flights

Thank you



University of California, San Francisco

